



# UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE  
United States Patent and Trademark Office  
Address: COMMISSIONER FOR PATENTS  
P.O. Box 1450  
Alexandria, Virginia 22313-1450  
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
-----------------	-------------	----------------------	---------------------	------------------

10/593,362

09/18/2006

Stefan Verseck

009848-0356699

1298

27500

7590

04/29/2010

PILLSBURY WINTHROP SHAW PITTMAN LLP

ATTENTION: DOCKETING DEPARTMENT

P.O BOX 10500

McLean, VA 22102

EXAMINER

JOIKE, MICHELE K

ART UNIT

PAPER NUMBER

1636

MAIL DATE

DELIVERY MODE

04/29/2010

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<p align="center"><b>Advisory Action</b> <b>Before the Filing of an Appeal Brief</b></p>	<b>Application No.</b> 10/593,362	<b>Applicant(s)</b> VERSECK ET AL.	
	<b>Examiner</b> Michele K. Joike	<b>Art Unit</b> 1636	

**--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

THE REPLY FILED 22 April 2010 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) ☐ The period for reply expires \_\_\_\_\_ months from the mailing date of the final rejection.  
 b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on \_\_\_\_\_. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

#### AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because  
 (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);  
 (b) ☐ They raise the issue of new matter (see NOTE below);  
 (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or  
 (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: \_\_\_\_\_. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).  
 5. ☐ Applicant's reply has overcome the following rejection(s): \_\_\_\_\_.  
 6. ☐ Newly proposed or amended claim(s) \_\_\_\_\_ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).  
 7. ☐ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.  
 The status of the claim(s) is (or will be) as follows:  
 Claim(s) allowed: \_\_\_\_\_.  
 Claim(s) objected to: \_\_\_\_\_.  
 Claim(s) rejected: 1-8, 10.  
 Claim(s) withdrawn from consideration: 9 and 11.

#### AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).  
 9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).  
 10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

#### REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see attached.  
 12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). \_\_\_\_\_.  
 13. ☐ Other: \_\_\_\_\_.

/Michele K. Joike/  
Primary Examiner, Art Unit 1636

Cont. of 11. Applicants argue that Nojiri et al do not teach a plasmid system with the alpha subunit and beta subunit on separate plasmids. There is also no suggestion to produce such a system. Nojiri et al would have had no motivation to modify their expression system since it was already producing large amounts of nitrile hydratase. The Examiner provides no explanation, but merely concludes that motivation somehow existed. Secondly, the specification teaches unexpected results. Nitrile hydratase activity increased more than eight times by having the alpha and beta subunits on separate plasmids, instead of on the same plasmid. Thirdly, the Examiner fails to explain how deleting the beta subunit from the plasmid containing both the alpha and beta subunits would increase beta subunit production, since fewer copies of the beta subunit would be available. Nishiyama et al fail to remedy the deficiencies of Nojiri et al.

Applicants' arguments are not persuasive for the following reasons. First of all the Examiner does not mention motivation because the TSM test (teaching, suggestion, motivation) is not the only rationale under KSR that can be used to establish a rejection under 35 U.S.C. 103(a). Secondly, it would have been obvious to one of ordinary skill in the art to not have the alpha and beta subunits on the same plasmid because Nojiri et al teach two separate plasmids, one with alpha and beta subunits and one with just the beta subunit. Therefore, having the alpha subunit on a plasmid, and having the beta subunit on a plasmid is known. Having just the beta subunit on a plasmid allows for expression of the subunit, in other words, there appears to be no difficulty in separating the two subunits. One of skill in the art knows that only one alpha subunit and one beta subunit is needed for nitrile hydratase to function, therefore it would be obvious to remove the beta subunit from the first plasmid. In fact, when both alpha and beta subunits were present together, the expression of the beta subunit was fairly low as compared to the alpha subunit. However, when beta was expressed separately on a plasmid, there was increased NHase activity. It is possible that increased activity was caused by the presence of an additional beta subunit. However, Nojiri et al teach that there were lower amounts of the beta subunit produced when alpha and beta were on the same plasmid, and that incorrect folding of NHase was partly due to the shortage of the beta subunit. While that would give the inventors a reason to have an additional beta subunit, it would also give the inventors a reason to explore why there were lower amounts of the beta subunit when it was on the same plasmid as the alpha subunit. Having the beta subunit on a separate plasmid is a logical choice, so is deleting the beta subunit on the plasmid with the alpha subunit, and placing a beta subunit on a separate plasmid to see if production is still affected is also a choice. There are a finite number of combinations of plasmids with subunits (alpha and beta on the same plasmid, alpha and beta on separate plasmids). A person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. In this case, it would have been obvious to try the alpha and beta subunits on separate plasmids in an attempt to improve production of the beta subunit. The fact that more than one alternative plasmid system exists does not mean that it would not be obvious to try a plasmid system with the alpha and beta subunits on separate plasmids. All of the claimed elements were known in the prior art and one skilled in the art could have separated the subunits by known methods with no change in their respective functions, and the separate plasmids, with each plasmid containing either the alpha or beta subunit, would have yielded predictable results to one of ordinary skill in the art at the time of the invention. Expressing the beta subunit on a separate plasmid increased NHase activity. Therefore one of skill in the art would have been motivated to separate the alpha and beta subunits in order to get better NHase activity and increased production of the beta subunit. Lastly, having nitrile hydratase activity increased more than eight times with the alpha and beta subunits on separate plasmids is not unexpected because Nojiri et al teach that the beta subunit on the same plasmid as the alpha subunit decreased production of the beta subunit, and having the beta subunit on a separate plasmid increased nitrile hydratase activity significantly. Having an additional beta subunit could increase production, but as just discussed, separating the beta subunit could also have affected activity. While the more than eight times activity is an improvement, it does not rise to the level of unexpected. There are no deficiencies for Nishiyama et al to cure, as just discussed.